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The role of thyroid stimulating hormone level as a predictive factor for advance stage thyroid carcinoma

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ABSTRACT

Thyroid stimulating hormone (TSH) is a cancer growth stimulus factor that have effect on the progression of thyroid carcinoma, common neck head malignancy. This hormonelevel has diagnostic value and can assist in the diagnosis, staging and management of the thyroid carcinoma. This study aimed to investigatethe role of TSH level as a predictor of advance stage thyroid carcinoma. This was case-control study involvingthyroid enlargement subjects who underwent thyroidectomy at Dr. Sardjito General Hospital, Yogyakarta from 2015 to 2017. Cancer staging examination using AJCC 2102 and TSH levels examination were conducted before underwent thyroidectomy. The inclusion criteria for case group were advanced stage (stage III and IV), while for control group wereearly-stage of thyroid carcinoma (stage I and II). The exclusion criteria for both case and control groups were 1) suffering from thyroid hormone disorders requiring therapy before thyroidectomy, 2) receiving thyroid suppression therapy prior to thyroidectomy. Sixty-six post thyroidectomy patients were involved in this study. The patients were divided into case and control groups consisted of 33 patients in each group. Based on receiver operating characteristic curve, the cut of point 1.27 mIU/L for TSH was obtained with sensitivity of 72.7% and specificity of 78.8%. There was statistically significant difference TSH levels between early stage thyroid carcinoma and late stage thyroid carcinoma (p = 0.001;OR: 9.9;95% CI: 3.19-30.15). It can be concluded that TSHlevels ≥ 1.27mIU/L as predictor of advance stage thyroid carcinoma.

ABSTRAK

Hormon perangsang tiroid (*thyroid stimulating hormone*/TSH) adalah faktor stimulus pertumbuhan kanker yang berpengaruh terhadapp progresivitas kanker tiroid, keganasan kepala leher yang sering terjadi. Nilai kadar hormon ini penting dalam membantu penegakan diagnosis, penentuan stadium dan tatalaksana karsinoma tiroid. Tujuan penelitian ini adalah mengkaji peran kadar TSH sebagai prediktor karsinoma tiroid stadium lanjut. Penelitian ini merupakan penelitian potong lintang yang melibatkan pasien karsinoma tiroid yang menjalani operasi tiroidektomi di RSUP Dr. Sardjito, Yogyakarta dari tahun 2015 sampai 2017. Pemeriksaan stadium karsioma dengan AJCC 2012 dan pemeriksaan kadar TSH dilakukan sebelum menjalani tiroidektomi. Kriteria inklusi kelompok kasus adalah karsinoma tiroid stadium lanjut (stadium III dan IV), sedangkan kelompok kontrol adalah stadium awal (I dan II). Kriteria eksklusi kedua kelompok kasus dan kontrol adalah 1) menderita gangguan hormon tiroid yang membutuhkan terapi sebelum tiroidektomi, 2) menerima terapi penekanan tiroid sebelum tiroidektomi. Enam puluh enam pasien pasca tiroidektomi terlibat dalam penelitian. Pasien dibagi menjadi kelompok kasus dan kontrol dengan setiap kelompok 33 pasien. Berdasarkan *receiver operating characteristic curve*, diperoleh nilai ambang batas kadar TSH 1,27 mIU/L dengan sensitivitas 72,7% dan spesivisitas 78,8%. Terdapat perbedaan nyata kadar TSH antara karsinoma tiroid stadium awal dan karsinoma tiroid stadium akhir (p = 0,001; OR: 9,9; 95% CI: 3,19-30,15). Dapat disimpulkan bahwa kadar TSH ≥ 1.27mIU/L merupakan prediktor karsinoma tiroid stadium lanjut.

Keywords:
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INTRODUCTION

Thyroid carcinoma is derived from two types of cells found in the thyroid gland. Follicular cells developing from endodermal can develop into papillary and follicular carcinomas. Cells derived from neuroendocrine-derived calcitonin-producing C cells can progress to medullary thyroid carcinoma. Thyroid lymphoma develops from the lymphoid tissue found in the thyroid tissue, while thyroid sarcoma originates from the connective tissue present in the thyroid.[1] Histopathological thyroid carcinoma classified as 78% papillary type, 13% follicular type, 2% anaplastic type and 4% medullary type.[2,3]

Thyroid cancer represents about 1% of new cancer diagnoses or 23,500 cases in the United States each year. Thyroid malignancy is divided into papillary carcinoma (80%), follicular carcinoma (10%), medullary thyroid carcinoma (5-10%), anaplastic carcinoma (1-2%), primary thyroid lymphoma (rare), and primary thyroid sarcoma (very rarely). Approximately 7-15% of thyroid nodules are malignant. Other disorders include various benign diagnoses, including colloid nodules, degenerative cysts, hyperplasia, thyroiditis, or benign neoplasms.[4] Incidence of disease is higher in women than men. A study conducted by Weir et al. from the Centers for Disease Control and Prevention (CDC), estimates that by the year 2020 the highest cancer incidence in women is one of them is thyroid carcinoma.[5]

Thyroid papillary carcinoma is the most common type of thyroid carcinoma. This type of carcinoma is 80% of the thyroid malignancy. Papillary carcinoma and follicular carcinoma are a differentiated carcinoma. Papillary carcinoma is a type of tumor with relatively slow growth. This tumor is derived from follicular cells that produce thyroxine (T4) and thyroglobulin (Tg) in the thyroid gland.[6]

The growth and development of thyroid carcinoma is influenced by oncogenes and various growth factors. Thyroid stimulating hormone (TSH) is a stimulus for cancer growth. This hypothesis is supported by the increased survival of patients with thyroid carcinoma treated with suppressive levothyroxine dose.[6,7] Itis known as a growth factor of thyroid carcinoma and plays an important role in the growth and progression of thyroid carcinoma. The TSH levels above the average population levels will generally increase the risk of malignancy of the thyroid gland.Thyroid stimulating hormone has a role in the process of carcinogenesis, although there are still some differences in views from some researchers. Some experts concluded that TSH receptor stimulation is associated with increased incidence of cancer and aggressiveness. Mutations in TSH receptors will affect the cAMP activation pathway (cyclic adenosine monophosphate) via G s. The fact that higher levels of TSH are significantly associated with increased risk of malignancy is strong evidence that TSH receptor stimulation is associated with thyroid carcinoma.[6]

Based on the above data it can be estimated that TSH, known as thyroid growth factor, also provides an important role in the growth, development and progression of thyroid carcinoma. The diagnostic value of TSH can be used to help determine the likelihood of stages of thyroid carcinoma, so that the management of thyroid nodules can be performed more optimally. The aim of this research was to investigate the cut of point TSH levels and contribution of others variable to advanced stage thyroid carcinoma.

MATERIALS AND METHODS

This was an observational analytic case-control study to determine the differences in TSH levels of patients with

early and advanced thyroid carcinoma undergoing thyroidectomy. The study was started after receiving approval from the Medical and Health Research Ethics Committee (MHREC) Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta (Ref. KE/FK/0494/EC/2018).

The study was performed from 2015 until 2017 on patients who had been diagnosed thyroid carcinoma based on histopathologic examination. The blood TSH levels were measured at least one week before thyroidectomy. High and low TSH levels were one of variables that affect early and advanced stage of thyroid carcinoma. The target population in this study were patients with thyroid carcinoma who underwent thyroidectomy. Affordable populations were thyroid carcinoma patients who undergo thyroidectomy at Dr. Sardjito General, Yogyakarta during 2015-2017 until the number of samples was fulfilled. The sample of the study was thyroid carcinoma patients undergoing thyroidectomy at Dr. Sardjito General Hospital, Yogyakarta in 2015-2017 until fulfilled number of samples that meet the criteria of inclusion and exclusion.

Population and samples

The inclusion criteria for case group were 1) patients post-operative anatomical pathology examination results of the diagnosis of thyroid carcinoma; 2) advanced stage of thyroid carcinoma (stage III and IV). While the inclusion criteria for control group were 1) patients with post-operative anatomical pathology examination results for the diagnosis of thyroid carcinoma; 2) early-stage of thyroid carcinoma (stage I and II). The exclusion criteria for case and control groups were 1) patients suffering from thyroid hormone disorders requiring therapy before thyroidectomy; 2) patients receiving thyroid suppression therapy prior to thyroidectomy. The sample of this research was thyroid enlargement patient in Dr. Sardjito General Hospital, Yogyakarta, which was calculated by the difference proportion formula, α:5%; β:20%, total sample were 66, that was 33 samples each group.

Statistical analysis

Differences in the proportion of the TSH levels between differentiated thyroid carcinoma groups and benign thyroid enlargement were analyzed using Chi square test, and then calculated the odds ratio (OR) and multivariate analysis. The cut-off point of TSH levels was determined using receiver operating characteristic (ROC) curve analysis. A p value < 0.05 was considered to be significant.

RESULTS

The subjects of this study were thyroid enlargement patients who underwent thyroidectomy at Dr. Sardjito General Hospital, Yogyakarta. Based on the results of physical and adjunctive examinations obtained from 2015 to 2017, patients with advanced stage thyroid carcinoma (stage III and IV) were included as case group and early stage (stage I and II) carcinoma patients were included as controls. There were 33 patients diagnosed as advanced stage (stage III and IV) carcinoma and 33 patients diagnosed as early stage (stage I and II) carcinoma. Histopathological examination of thyroid tissue after thyroidectomy was performed in the Department of Anatomical Pathology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta. Characteristics of the subjects of this study include gender, age, and histopathology, is presented in TABLE 1.

TABLE 1. Characteristics of research subjects

Characteristic	Stage I and II [n (%)]	Stage III and IV [n (%)]	Total [n (%)]	p
Sex				
• Male	10 (30.3)	6 (18.2)	16 (24.2)	0.389
• Female	23 (69.7)	27 (81.8)	50 (75.8)	
Age				
• < 45 years old	20 (60.6)	0 (0.0)	20 (30.3)	0.001
• ≥ 45 years old	13 (39.4)	33 (100)	46 (69.7)	
Histopathological				
• Papillary carcinoma	31 (93.9)	27 (81.8)	58 (87.9)	0.324
• Follicular carcinoma	2 (6.1)	3 (9.1)	5 (7.6)	
• Undifferentiated	0 (0.0)	2 (6.1)	2 (3.0)	
• Hurtle cell carcinoma	0 (0.0)	1 (3.0)	1 (1.5)	

There was no statistically significant difference (p=0.389) in sex distribution group sample between case and control groups (TABLE 1). The results of this study were similar to Haymart *et al.*[6] which obtained 80.7% of female thyroid enlargement patients and 19.3% of male with the ratio between femaleand male was 4.2:1. In addition, Boelaert *et al.*[7] reported the ratio between male and female was 8:1.

The greatest age frequency in the age group ≥45 were 46 (69.7%) people (TABLE 3). By Fisher's analysis exact test was found statistically significant difference in age between case group and control group (p= 0.001). This result is similar to Haymart *et al.*[6] study, the age frequency of patients with the greatest thyroid enlargement is 45-50 years. Boelaert *et al.*[7] reported that the peak incidence of patients with thyroid enlargement was 48-50 years.

All patients with undifferentiated carcinoma histopathology were present in the case group (stage III and IV). A retrospective cohort studies conducted in the United States reported that distribution of histologic categories of thyroid cancer i.e. 88% papillary carcinoma, 9% follicular carcinoma and 3% were poorly differentiated.[8]

The main outcome in this study was to evaluate the relationship between TSH levels and stage of thyroid carcinoma. High and low levels of TSH are determined based on the cut-off point of TSH levels obtained through receiver operating characteristic (ROC) curve analysis (FIGURE 1). The cut-off point TSH level based on receiver operating characteristic analysis curve was 1.27 mIU/L with a sensitivity value of 0.727 (72.7%) and a specificity value of 0.788 (78.8%). Value area under the curve (AUC) 0.826 with p value = 0.001. Based on the cut of point value, TSH levels can be categorized as low TSH levels when <1.27 mIU/L and high TSH levels when ≥ 1.27 mIU/L.

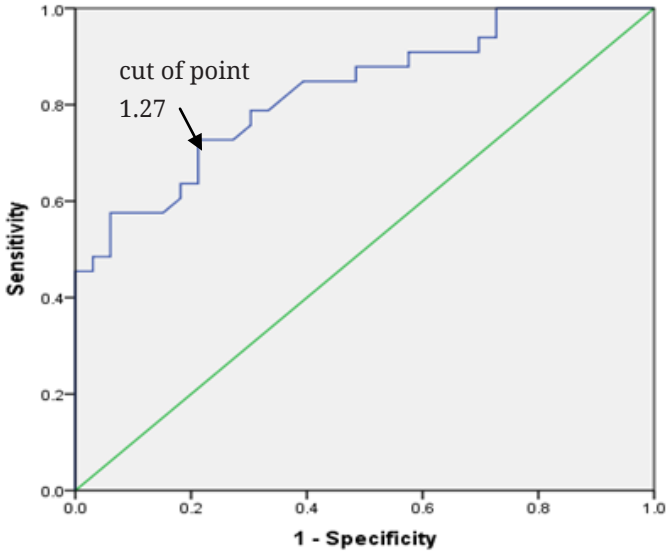

FIGURE 1. Receiver operating characteristic (ROC) curve analysis of TSH

TABLE 2. Analysis of TSH levels on case and control groups

TSH level	Stage I and II [n (%)]	Stage III and IV [n (%)]	p	OR (95% CI)
Low TSH	26 (78.8)	9 (27.3)	0.001	9.9 (3.19-30.15)
High TSH	7 (21.2)	24 (72.7)		

TABLE 2 shows that there was significantly difference between the TSH levels of the case and control groups by using cut off 1.27 m IU/ L (p = 0.001;OR: 9.9; 95% CI: 3.19-30.15). Thyroid enlargement patients with high TSH levels were at 9.9 times more likely to have advanced stage (stage III and IV) than patients with thyroid carcinoma with low TSH levels.

TABLE 3. Logistic regression analysis contribution independent variables

Variable	β	p	OR	95%CI
TSH	2.94	0.009	18.93	2.09-171.30
Age	0.19	0.001	1.21	1.09-1.34
Sex	1.09	0.343	2.96	0.31-27.93

TABLE 3 show the logistic regression analysis was done to determine the contribution of variable to the stage of thyroid carcinoma. Result of this study showed that TSH and age were significantly play a role in the stage of thyroid carcinoma, with p value of 0.009 (OR: 18.9; 95% CI: 2.09-171.3) and 0.001 (OR: 1.21; 95% CI: 1.09-1.34) respectively, while sex was not significantly play role (p = 0.343; OR: 2.96; 95%CI: 0.31-27.93). Gul *et al.*[9] reported multivariate analysis of the variables that affect the thyroid malignancy. These variables included nodule type and TSH levels, free T3 and free T4. This study did not directly determine the association of TSH levels with nodule types. It was concluded that TSH is an independent risk factor for thyroid malignancy separate from the nodule type.

DISCUSSION

TSH is a hormone that plays a role in stimulating the occurrence of hormone synthesis in the thyroid gland. TSH is one of four hormones produced by the anterior pituitary gland, with a molecular weight of about 26,000-28,000 daltons. TSH production occurs by stimulation of thyrotropin releasing hormone (TRH), produced by the hypothalamus which then stimulates the pituitary gland to produce TSH. Under normal circumstances, levels of TSH present in the body range from 0.5-5 mIU/L. Patients with euthyroid have levels of 1 mIU/L TSH.[10-12]

The incidence of thyroid carcinoma has tripled in the last three decades with increasing demographics and access to health care, resulting in more diagnosis being enforced. The mortality rate of thyroid carcinoma is relatively stable over this time period.[13] The incidence of these carcinomas may be familial, either self-occurring or associated with Gardner's syndrome (familial adenomatous polyposis). Radiation exposure especially during childhood is associated with thyroid papillary carcinoma. Tumors generally appear after a latent phase between 10-20 years. Increased incidence of thyroid papillary carcinoma is elevated in patients suffering from Hashimoto's thyroiditis (chronic lymphocytic thyroiditis). But the incidence of this carcinoma in nodules was found in patients with Hashimoto's thyroiditis and patients with the same normal thyroid.[14]

In differentiated thyroid carcinomas the value of TSH usually depends on the severity of the cancer. Almost all patients are expected to be around 0.1 - 0.5 mIU/L. Then performed thyroid function tests and Tg, 8 weeks postoperatively.[15,16] If not detected Tg, do the examination 6 months later in the form of neck examination and thyroid function examination. The examination was continued 1 year later with scan and Tg. When the scan is negative and Tg <2 ng/mL, followed by 6 months interval for physical examination, thyroid function, Tg and ultrasound. After that monitoring was done 5 years later and there after followed annually.[12,17]

Risk factors associated with thyroid carcinoma include radiation exposure. The type of thyroid carcinoma associated with radiation exposure is papillary carcinoma. Specific radiation of the thyroid gland (thyroid ablation therapy with I131) or high-dose external-beam radiation therapy does not increase the risk of incident papillary thyroid carcinoma. At this dose of therapy most of the exposed cells will die. Populations with low iodine diarrhea are associated with the incidence of follicular and anaplastic carcinomas.[1]

Papillary carcinoma is a type of tumor with relatively slow growth. This tumor originates from the follicular cells that produce T4 and Tg in the thyroid gland. These cells are highly sensitive to TSH and take-up iodine. This provides a diagnostic and therapeutic value for

the treatment of residual disease and recurrence, after surgical treatment.[18] Follicular carcinoma is the second most common malignancy after thyroid papillary carcinoma. This cancer covers 10% of all thyroid malignancies. This carcinoma shows an increased incidence in areas with low iodine intake. As with thyroid papillary carcinoma, thyroid solid carcinoma occurs more in females than males, with a ratio of 3:1.[14,18]

Patients with thyroid follicular carcinoma possess older age characteristics compared with patients suffering from thyroid papillary carcinoma in general. The average age is the 4th and 5th decades. Thyroid follicular carcinoma develops from thyroid follicular cells. These neoplasm cells depend on TSH, or are said to be sensitive to TSH, absorbing iodine and producing Tg.[18]

The signs and symptoms of thyroid carcinoma on clinical examination manifest as thyroid nodules, usually solid, painless, palpable. These nodules are often found on palpation of the neck. On physical examination palpable nodules usually in patients older than 60 years or younger than 30 years. If the nodule is found in men, the risk of malignancy will be higher. In thyroid malignancy is often found rapid growth of nodules, although usually does not feel pain. If any sudden onset of pain may be associated with benign lesions of the thyroid such as: thyroid bleeding or acute thyroiditis.[1,14]

There are no symptoms that are typical for thyroid cancer, patients generally come with a painless lump in the neck. Anamnesis in patients with thyroid carcinoma most patients come with complaints of a lump on the anterior neck. Lumps caused by malignancy need to know risk factors such as; radiation history, family history, geography and settlement environment. Rapid growth with emphasis on surrounding organs or tissues can be a marker. In anaplastic type, growth is usually very rapid and followed by pain especially in elderly patients followed by changes in sound, difficulty swallowing and shortness of breath as a sign of tissue invasion or surrounding organs (recurrent nerves, esophagus and trachea).[15]

Investigations performed according to the guidelines of the UK Association of Thyroid Cancer (United Kingdom), are advised to perform thyroid function tests (TFTs) first in patients with thyroid nodules. The results of these checks are used to determine the intended referrals. If the euthyroid with suspected thyroid nodules are malignant, then referred to the cancer handling team. A hypothyroid and hyperthyroid state is not necessarily a malignancy, as differentiated cancer cells also have the ability to capture iodide and produce Tg. In some cases differentiated thyroid cancers have been reported thyrotoxicotic conditions.[2,15,16] Examination of thyroid gland function includes examination of levels of TSH, T4, T3, Tg, and calcitonin. Examination of Tg levels is used to evaluate the outcome of a therapy and the occurrence of recurrence in patients with thyroid cancer. Calcitonin may be a marker of medullary thyroid cancer, where laboratory tests are performed when anamnesis is found to have a family history and may be a routine examination.[2,16]

According to Zhang *et al.*[19] diagnosis and management of differentiated thyroid carcinoma based on the American Thyroid Association guidelines in 2009, Bethesda's system for thyroid cytopathology classification as well as current examination of molecular cytology with fine needle aspiration (FNA). Any symptomatic thyroid lump should be examined for TSH and thyroid ultrasound. Uptake thyroid examination is performed after TSH examination. Patients with hyperfunction nodules are referred to endocrine experts and not recommended for FNAs.

Thyroid carcinoma is the most

frequent endocrine neoplasm and mutation at the frequent thyrotropin receptor (TSHR). Some theories explain the process of carcinogenesis of thyroid carcinoma. Several theories are related to the role of TSH in the process of carcinogenesis and its progression. Several genes and structural proteins are involved in the TSHR mutation. Theories include cancer stem cell theory and classical theory. TSHR changes in thyroid cancer that play a role in the process of thyroid carcinogenesis associated with genetic instability during evolution. However the presence of functional TSHR is utilized in therapy. Epigenetic concepts also play a role in this process.[20]

TSH will induce the occurrence of cancer along with other growth factors. Chronic stimulation of TSH is an important carcinogenesis factor. The role of TSH receptors and TSH receptor mutations is known to play a role in the incidence of thyroid carcinoma. Genetic change is a risk factor for malignant growth in the thyroid.[6] TSH activates the transmembrane-G protein receptor on the surface of follicle cell, and induces the production of intracellular cyclic AMP (cAMP). This process is carried out by the enzyme adenylate cyclase. The cAMP molecule will stimulate the cAMP-dependent kinase A (PKA) protein, which will phosphorylate the cytoplasmic proteins and target proteins in the cell nucleus.[21]

The determination of the thyroid stage adheres to the TNM system, determined by primary tumor (T), lymph node metastasis (N), and distant metastasis. The higher levels of TSH are associated with the higher stage of thyroid cancer. Based on these data above serum TSH levels have an important role in the growth and development of thyroid carcinoma. TSH has been recognized as a growth factor of nodules in the thyroid, and suppression of TSH levels by giving exogenous thyroid hormone will inhibit the growth of existing nodules and inhibit the growth of new nodules.[7]

Ongoing TSH stimulation can change slowly differentiated thyroid carcinomas that grow rapidly and metastasize. Increased levels of TSH will increase the growth of thyroid carcinoma and TSH suppression therapy will decrease the size and decrease the rate of recurrence of differentiated thyroid carcinomas.[22,23] Differentiated thyroid tumors express TSH receptors in the plasma membrane. TSH will increase adenylate-cyclase activity which will increase cAMP production and cell growth through TSH receptors on in vitro examination.[6,7]

TSH is the main regulator of thyroid hormone production by follicular cells of the thyroid gland. Although TSH is not the only growth factor in thyroid tumors, TSH has an important role in the network of signals that modulate the growth of thyroid gland cells and their function. TSH has a role not only in the control of differentiation functions such as expression of thyroid-specific genes, but also regulates expression of growth factors and receptors.[24] These growth factors and receptors include: epidermal growth factor receptor, insulin-like growth factor-1-dependent signal, and insulin. TSH has also been reported as a mitogen in the proliferation of thyroid carcinoma cells. All papillary and follicular thyroid carcinomas express TSH receptor at varying amounts.[19,24,25]

The state of thyroid function of the thyroid is not affected by TSH levels called autonomic thyroid function (TSH <0.4 μIU/mL) is associated with a reduced risk of papillary thyroid carcinoma. Some studies support higher levels of TSH, although still within the normal range, associated with thyroid cancer in patients with thyroid gland enlargement.[26] The study in the number of research subjects 247, assessed the association of TSH levels and extension of extrathyroidal tumors and tumor size. This study concluded that there was a significant difference mean of TSH

level between subjects with extrathyroid extension compared with subjects without extension of extrathyroid with different grade of TSH 3.59 (p= 0.004). In the same study, there was no significant difference in TSH levels between thyroid carcinoma with tumor size >4cm compared to <4cm with mean difference value of TSH level 0.17 (p = 0.89).[6]

The prognosis of patients with differentiated thyroid carcinomas depends on the staging and therapy given. The choice of therapy is determined by staging of thyroid carcinoma. Some patients with higher stages require additional therapy such as neck dissection or ablation therapy. In this system, the stage depends on the patient's age. Patients over the age of 45 will have a higher relative stage than patients under 45 years of age at the time of diagnosis. The 5-year survival rate was 99% and the 10-year survival rate was 98%.[12]

CONCLUSION

There is a significant difference of TSH levels between early (stage I and II) and advanced stage carcinoma (stage III and IV). The TSH more than 1.27 mIU/L can be considered as predictor for advance stage thyroid carcinoma.

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